

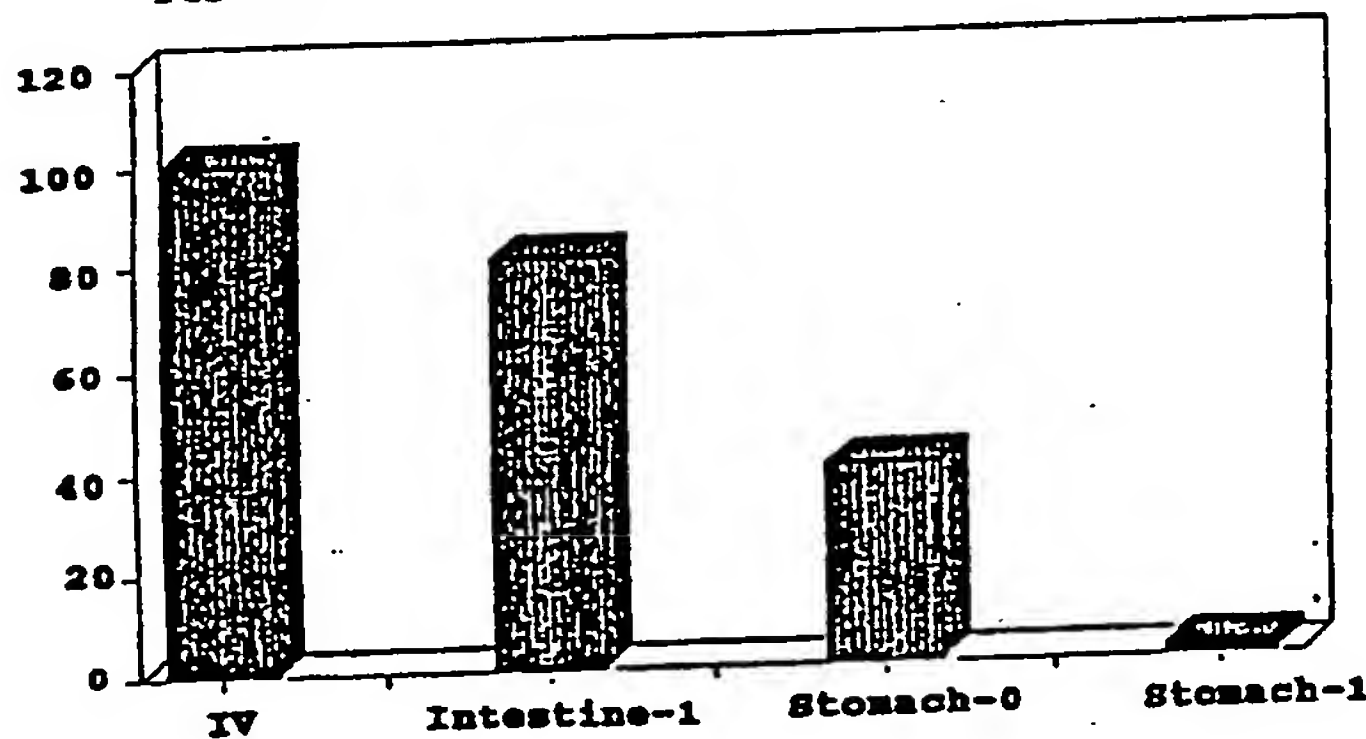


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(54) Title: ORALLY ADMINSTRABLE GALLIUM COMPOSITIONS AND METHODS OF TREATMENT THEREWITH

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(57) Abstract

Orally administrable gallium compositions are disclosed comprising a gallium complex in which each ligand is provided by the same or a different compound selected from the group consisting of 3-hydroxy-4-pyrones in which one or more of the hydrogen atoms attached to ring carbon atoms are optionally replaced by a hydrocarbon group of 1 to 6 carbon atoms, wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine. The compositions are used in the treatment of bone calcium disorders, for chemotherapeutic purposes and for radiographic imaging.

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ORALLY ADMINISTRABLE GALLIUM COMPOSITIONS AND METHODS
OF TREATMENT THEREWITH

FIELD OF THE INVENTION

The present invention relates to the field of pharmaceuticals, generally, and in particular to pharmaceutical compositions containing gallium and their use in the treatment of bone calcium disorders, the treatment of certain cancerous conditions, and the diagnosis of various conditions through the use of radiodiagnostic techniques.

BACKGROUND OF THE INVENTION

Gallium is a metal which belongs to the Group IIIa elements of the periodic table. By mechanisms which are still uncertain, radioactive gallium salts are known to accumulate in certain tumors. ⁶⁷-Gallium citrate has been used for diagnostic purposes in patients with bone infections and malignant diseases. In 1952, King et al., (Arch. Int. Med. 90:785 (1952)) first showed that injections of highly radioactive gallium caused tumor regression in cancer patients. U.S. Patent No. 4,303,636 discloses a method of cancer treatment which uses radioactive ⁶⁷-gallium, as a cytotoxic agent. Non-radioactive salts of gallium and other Group IIIa metals were first evaluated for their anticancer activity in 1971 and gallium was found to be the most potent and least toxic element for reducing the size of animal tumors. Gallium nitrate entered into clinical trials as a cytotoxic anticancer agent in 1976.

Gallium has been known for many years to be useful in the treatment of calcium bone disorders. U.S. Patent No. 4,529,593 teaches the use of pharmaceutically acceptable gallium salts to reduce the excessive loss of bone calcium. That patent specifically teaches the use of gallium to prevent or treat disorders associated with extensive loss of calcium from bone in humans by administering to the individual a pharmaceutically acceptable gallium compound. Of especial importance among the disorders which may be thus prevented or treated are hypercalcemia, osteopenia, osteoporosis, bone destruction due to metastasis from

malignant tumors, and hyperparathyroidism. Gallium salts which are disclosed to be of use include the nitrate, citrate, and halide, preferably the chloride, carbonate, acetate, tartrate, oxalate, oxide or hydrated oxide.

For the non-invading nuclear medical diagnosis of cancer or tumor, there is ordinarily used gallium citrate ⁶⁷-Ga. For example, in U.S. Patent No. 4,479,913 there is described an apparatus and method for diagnosing ocular cancer in which the radiation level produced in each eye is measured after the administration of a tumor-localizing radiopharmaceutical, such as gallium-67. Determination of a malignancy is based on the detection of increased radioactive uptake in the area of the tumor.

In all of the foregoing applications of gallium, the active compound typically has been administered intravenously. Although there has been discussion in some of the references about the oral administration of the gallium compounds discussed therein, no effective means of oral administration has heretofore been employed. Obviously, it would be very desirable to administer the gallium for the aforementioned purposes through an oral route, but the gallium compounds previously used pharmaceutically have not been absorbable through oral administration.

U.S. Patent No. 4,596,710 relates to the application of gallium chloride as drug particularly useful for the treatment of malignant tumors, and to the pharmaceutical compositions purportedly intended for oral administration. The anti-tumoral effect of gallium chloride in female dogs having spontaneous malignant tumors of the breast is disclosed. The gallium chloride was administered in the form of drinkable ampoules. Also, the use of gallium chloride in the treatment of malignant tumors of the genital tracts, administered by the oral route, is disclosed. To date, however, acceptance of the oral administration of gallium chloride for such treatment has not existed. It is

not known if that has been due to problems with the oral administration of the gallium chloride or due to other reasons. In any event, the oral administration of gallium chloride has not, to date, become an acceptable means of treatment of malignant tumors.

The preparation of complexes of gallium with 3-hydroxy-4-pyrones has been discussed in the literature (Finnegan et al., Inorganic Chemistry, Vol.26, no. 13, pages 2171-2175, (1987)). Further, the tissue distribution of the gallium maltol complex has been studied (Farrar et al., Journal of Food Chemistry Toxicology, vol. 26, no. 6, pages 523-525, (1988)). The gallium maltol complex, administered directly to the stomach of fasted rats, was found to have an increased uptake into various vital organs, when compared to noncomplexed gallium, but no difference was seen with fed rats. The absorption of the gallium maltol, even in the fed rat, was not sufficient to be of clinical utility.

SUMMARY OF THE INVENTION

It has now been surprisingly found that gallium can be readily administered orally for use in the treatment of bone calcium disorders, for chemotherapeutic purposes and for radiographic imaging. In accordance with the present invention, certain gallium compounds are used for the first time in such pharmaceutical applications by protecting the compositions from dissociation in the stomach while allowing for their release in the intestines.

While previously it has been impossible to orally administer gallium in adequate pharmaceutical doses, it has now been discovered that such oral administration can be achieved. It has been discovered that certain gallium complexes can be absorbed in adequate pharmaceutical doses provided that such complexes are protected from destruction in the stomach and are formulated to be released in the intestine.

The gallium compositions of the present invention thus provide for ease of administration, because they may be

administered orally, whereas gallium compositions used previously in similar applications have typically required intravenous or intramuscular administration.

Also, because of the particular solubility characteristics of the gallium compounds used in the present invention, the compounds have the potential to penetrate into regions of the body which were inaccessible to the previously employed gallium compounds.

The gallium compounds of use comprise the gallium complexes of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a hydrocarbon group of 1 to 6 carbon atoms.

The present invention particularly relates in part to the pharmacologic use in humans and animals of the aforementioned pharmaceutically acceptable gallium compositions in non-nephrotoxic amounts to inhibit resorption of calcium from bone in patients with hypercalcemia, bone fragility or other disorders associated with abnormally increased calcium resorption, by administering to a patient suffering from one of those conditions a therapeutically effective amount of such a compound. The gallium compounds may also be used to treat disorders associated with extensive loss of calcium from bone in a human by administering to the patient a therapeutically effective amount of one of the aforementioned gallium compositions.

Further, the present invention provides a method for the treatment of malignant tumors, particularly tumors of the breast and the genital tracts, by administering a therapeutically effective amount of one of the aforementioned gallium compositions.

Additionally, the gallium compounds may be used as radiodiagnostic agents to detect the presence of tumors and the like, by administering such compositions to an individual and then determining if the gallium has been

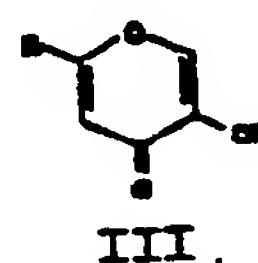
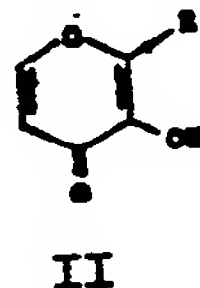
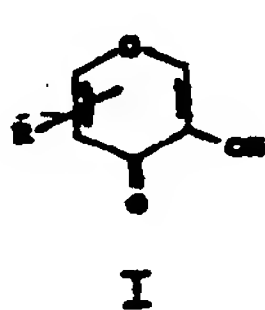
selectively bound to a localized region of the body, signifying the possible presence of a tumor.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

THE GALLIUM COMPLEXES

As indicated, the present invention relates to the use of compositions comprising certain gallium compounds in several pharmaceutical applications. The compounds employed in the present invention are of particular interest because of their ability to be usefully absorbed into a patient's bloodstream and distributed throughout the body, after oral administration. In the past, gallium compounds have been employed in the same or similar applications, but have been hindered by the need to administer the compounds through intravenous injection, or the like.

The ability of the gallium compositions of the present invention to be usefully administered orally stems in part from the chemical composition of the ligands which are complexed with the gallium. The hydroxypyrones providing ligands which may be used in complexes according to the present invention all have the general formula (I), and those of particular interest also have the specific formula (II) or (III):



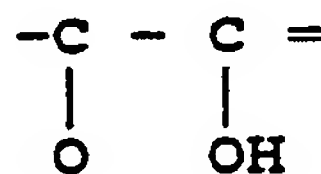
in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms. The hydrocarbon groups may optionally contain heterologous atoms, such as oxygen, sulfur, or the like and may thus include functional groups such as esters, ethers, ketones, and the like. Preferably R represents an aliphatic group, most preferably an alkyl group, for example methyl, ethyl, n-propyl isopropyl or butyl. As the presence

of one or more R groups is optional, n may be 0, 1, 2 or 3 (the ring being unsubstituted by any hydrocarbon group when n is 0).

Among the compounds of the foregoing structures, maltol, 3-hydroxy-2-methyl-4-pyrone (formula II, R = CH₃) is of most interest. Pyromeconic acid, 3-hydroxy-4-pyrone (formula I, n = 0), 3-hydroxy-6-methyl-4-pyrone (formula III, R = CH₃) and ethyltpyromeconic acid, 2-ethyl-3-hydroxy-4-pyrone (formula II, R = C₂H₅) may also be of special interest.

The substituted 3-hydroxy-4-pyrones may carry more than one type of hydrocarbon group but this is not usual and, indeed, substitution by one rather than two or three hydrocarbon groups is preferred. When the R group represents an aliphatic hydrocarbon group, the same may be cyclic or acyclic, having a branched chain or especially a straight chain in the latter case, and may be unsaturated or especially saturated. Groups of from 1 to 4 carbon atoms and particularly of 1 to 3 carbon atoms are of most interest. Alkyl groups are preferred, for example cyclic groups such as cyclopropyl and especially cyclohexyl, but more particularly preferred are acyclic alkyl groups such as n-propyl and isopropyl, and especially ethyl and methyl.

Substitution with an R group at the 2- or 6-position is of special interest although, when the ring is substituted by the larger aliphatic hydrocarbon groups, there may be an advantage in avoiding substitution on a carbon atom alpha to the



system. This system is involved in the complexing with gallium and the close proximity of one of the larger aliphatic hydrocarbon groups may lead to steric effects which inhibit complex formation.

In the case of certain of the hydroxypyrones referred to above, for example maltol, the formation of a gallium complex of the compound has been referred to in the literature. In the case of other hydroxypyrones, the gallium complexes are novel and are included, per se, by the present invention.

The gallium complexes are conveniently prepared by the reaction of the hydroxypyrene and gallium ions, the latter conveniently being derived from a gallium salt, particularly a gallium halide and especially gallium chloride. The reaction is conveniently effected in a suitable mutual solvent and water may often be used for this purpose. If desired, however, an aqueous/organic solvent mixture may be used or an organic solvent, for example ethanol, methanol or chloroform and mixtures of these solvents together and/or with water where appropriate. In particular, methanol or especially ethanol may be used where it is desired to effect the separation of at least a major part of a by-product such as sodium chloride by precipitation while the gallium complex is retained in solution.

Reaction to form the gallium complex is generally rapid and will usually have proceeded substantially to completion after 5 minutes at about 20° C., although a longer reaction time may be used if necessary. Following separation of any precipitated by-product, such as sodium chloride in the case of certain solvent systems, the reaction mixture may conveniently be evaporated on a rotary evaporator or freeze dried to yield the solid gallium complex. This may, if desired, be crystallized from a suitable solvent, for example water, an alcohol such as ethanol, or a solvent mixture, including mixtures containing an ether.

Certain hydroxypyrones, such as maltol, are available commercially. With others, a convenient starting material in many instances consists of pyromeconic acid which is readily obtainable by the decarboxylation of meconic acid.

Thus, for example, pyromeconic acid may be reacted with an aldehyde to insert a 1-hydroxyalkyl group at the 2-position, which group may then be reduced to produce a 2-alkyl-3-hydroxy-4-pyrone. It will be appreciated that these are not the only routes available to these compounds and their gallium complexes and that various alternatives may be used as will be apparent to those skilled in the art.

PHARMACEUTICAL USES

The present invention relates in part to the pharmacologic use in humans and animals of the aforementioned pharmaceutically acceptable gallium compounds in non-nephrotoxic amounts to treat bone calcium disorders. In the treatment of one class of bone calcium disorder the gallium compounds are used to inhibit resorption of calcium from bone in patients with hypercalcemia, bone fragility or other disorders associated with abnormally increased calcium resorption, by administering to a patient suffering from one of those conditions a therapeutically effective amount of such a compound. In the treatment of another class of bone calcium disorder, the gallium compounds are used to prevent extensive loss of calcium from bone in a human by administering to the patient a therapeutically effective amount of one of the aforementioned gallium compounds.

In the treatment of the aforementioned calcium bone disorders, the gallium complexes used in the treatment of such disorders are made with nonradioactive gallium. The compositions are administered orally in sufficient therapeutic quantity to effectively treat the disease. Typically, the quantities administered will be sufficient to maintain a serum blood level in the patient of from about 0.1 to about 5.0 micrograms of gallium per ml of blood, preferably from about 0.5 to about 2.0 micrograms of gallium per ml of blood. Such blood levels may be achieved by administering from about 0.1 to about 20 grams of gallium per day to the patient.

For the treatment of various forms of cancer, especially malignant tumors, particularly of the breast and genital tract, the gallium complexes of the present invention are employed wherein the gallium may or may not be radioactive, such as gallium-67. For purposes of treating the cancerous condition, it is typical to administer quantities of gallium in the range of from about 0.5 mg of gallium per kilogram of body weight to about 5.0 mg of gallium per kilogram of body weight, per day, for a sufficient period of time to achieve a therapeutic effect on the cancerous condition.

Because of the unique solubility properties of the complexes of the present invention, the complexes have the ability to reach areas previously inaccessible to other gallium compositions. Thus, the complexes used in accordance with the present invention may permeate the blood-brain barrier, making them useful for the treatment of tumorous conditions of the brain.

Additionally, the gallium complexes of the present invention may be used as radiodiagnostic agents to detect the presence of tumors and the like. The complexes, for such a purpose, is made with radioactive gallium (gallium-67). The complexes are administered to an individual and then a determination is made as to whether such compounds have been selectively bound to a localized region of the body, signifying the possible presence of a tumor. Again, because the solubility characteristics of the presently employed compounds may allow for the permeation of the gallium across the blood-brain barrier, the gallium complexes may be useful in the detection of tumorous conditions of the brain.

The method of detecting localized concentrations of radioactivity is well known in the art. As one example, one type of apparatus and method used to detect ocular tumors is described in U.S. patent no. 4,448,763. After administering

the gallium-67 complex, the radiation level in both eyes are measured and compared.

The quantity of gallium complex administered for the purpose of radiodiagnostically determining the presence of a tumor is not critical. Typically from about 100 mg to about 1000 mg of gallium is administered for such purposes. Because the gallium has been found to preferentially bind to tumorous cells, a localized concentration of radiation after the gallium complex has been allowed to distribute throughout the body, may be indicative of a tumorous condition.

In accordance with U.S. Patent No. 4,448,763, it is known that nonradioactive indium is capable of altering the distribution of gallium in the blood. Thus, indium competes with gallium for blood and soft tissue binding sites, yet does not compete for gallium binding sites in tumors. Therefore, in accordance with the present invention, it is also contemplated that the gallium complexes used in accordance with the present invention may be administered with indium, as taught in the aforementioned U.S. Patent No. 4,448,763, which is hereby incorporated by reference. As taught in that patent, the indium may be administered before, concurrent with, or after the administration of the gallium complexes of the present invention. If administered before or after, it is preferably administered within two hours before or after the administration of the gallium complex. Indium may therefore be used as an adjunct in both the use of gallium complexes to treat cancerous conditions, and in the use of the gallium complexes as radiodiagnostic agents.

PHARMACEUTICAL FORMULATIONS

The gallium complexes may be formulated for use as pharmaceuticals by a variety of methods. Where desired, more than one hydroxypyrrone gallium complex as described above may be present in the pharmaceutical composition.

Although compositions incorporating a liquid diluent may be used for oral administration, it is preferred to use compositions incorporating a solid carrier, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate. The gallium complex will of course be present in such a preferred composition in solid form, which form is accordingly a preferred one for the complex, and such a solid composition may conveniently be presented as some type of formed composition, for example as tablets, capsules (including spansules), etc.

One of several approaches may be employed to avoid or reduce exposure of the gallium complex to the acidic conditions of the stomach and to allow the release of the gallium compounds in the intestine. Such approaches may involve various types of controlled release system, ranging from one, which may for example be based on a polymer, which simply provides a delayed release of the complex with time, through a system which is resistant to dissociation under acidic conditions, for example by the use of buffering, to a system which and is biased towards release under conditions such as prevail in the small intestine, for example a pH sensitive system which is stabilized towards a pH of 1 to 3 such as prevails in the stomach but not one of 7 to 9 such as prevails in the small intestine. Since the pH of the stomach is higher after a meal, it may be advantageous, whatever method of formulation is used, to administer the gallium complexes at such a time.

A particularly convenient approach to a controlled release composition involves encapsulating the gallium complex by a material which is resistant to dissociation in the stomach but which is adapted towards dissociation in the small intestine (or possibly, if the dissociation is slow, in the large intestine). Such encapsulation may be achieved with liposomes, phospholipids generally being resistant to dissociation under acidic conditions. The liposomally entrapped complexes can therefore survive the acid

environment of the stomach without dissociating. On entry into the small intestine, the pancreatic enzymes rapidly destroy the phospholipid-dependent structure of the liposomes thereby releasing the complex. Liposome disruption is further facilitated by the presence of bile salts. However, it is usually more convenient to effect the encapsulation, including microencapsulation, by the use of a solid composition of a pH sensitive nature.

The preparation of solid compositions adapted to resist dissociation under acidic conditions but adapted towards dissociation under non-acidic conditions is well known in the art and most often involves the use of enteric coating, whereby tablets, capsules, etc, or the individual particles or granules contained therein, are coated with a suitable material. Such procedures are described, for example, in the article entitled, "Production of Enteric Coated Capsules" by Jones in *Manufacturing Chemist and Aerosol News*, May 1970, and in such standard reference books as Pharmaceutical Dosage Forms, Volume III by Liebermann and Lackmann (published by Marcel Decker).

One particular method of encapsulation involves the use of gelatine capsules coated with a cellulose acetate phthalate/diethylphthalate layer. This coating protects the gelatin capsule from the action of water under the acid conditions of the stomach where the coating is protonated and therefore stable. The coating is however destabilized under the neutral/alkaline conditions of the intestine where it is not protonated, thereby allowing water to act on the gelatin. Once released in the intestine the rate of permeation of the intestine wall by the water soluble complex is relatively constant irrespective of the position within the intestine, i.e. whether in the jejunum, ileum or large intestine. Other examples of methods of formulation which may be used include the use of polymeric hydrogel formulations which do not actually encapsulate the gallium

complex but which are resistant to dissociation under acidic conditions.

A second approach to countering the effect of the acidic conditions prevailing in the stomach involves formulation of the complex in the pharmaceutical composition together with the metal-free hydroxypyrrone from which it is derived. The dissociation of the complex, for example, involves various equilibria between the complex, and the metal-free compound, so that the presence of the latter will inhibit this dissociation. Any proportion of the free compound can be advantageous in this context but little further advantage accrues from increasing the proportion beyond a certain level. A preferred range for the molar proportion of the free compound present in compositions according to the present invention is thus from 0 to 100 moles of free hydroxypyrrone:1 mole of gallium complex.

Conveniently, a proportion of up to no more than 20, 30 or 50 moles:1 mole is used with a lower level of 0.5, 1 or 2 moles:1 mole. Although to obtain a marked effect upon dissociation of the gallium complex a proportion of at least 5 or 10 moles:1 mole is usually employed, it should be emphasized that even a molar ratio such as 1:1 will achieve a noticeable degree of acid stabilization of the gallium complex. Thus although a range of, for example, from 10 moles:1 mole to 20 moles:1 mole of metal-free hydroxy pyrrone:gallium complex will often be suitable to produce a marked effect, a range of, for example, 3 or even 1 mole:1 mole to 10 moles:1 mole will still produce a worthwhile effect without requiring administration of the larger amounts of the hydroxy pyrrone.

Although solid compositions are preferred in many applications, liquid compositions are of interest in certain particular instances. It is often desirable to produce liquid compositions containing a higher concentration than is readily obtainable with a purely aqueous composition or indeed one containing organic solvents such as simple

monohydric alcohols. It has been found that this may be done by the use of solvents containing two or more hydroxy groups or a hydroxy and an ether group, especially of glycols or glycol ethers, either in admixture with water or, for better solubilization, alone. The glycol ethers of particular interest are the mono-ethers containing as an etherifying group an aliphatic hydrocarbon group of 1 to 6 carbon atoms as described above, for example a methyl group, such a glycol mono-ether being methyl ethylene glycol. In general, however, the glycols themselves are preferred. Examples of such glycols are the simple dihydroxy alkanes such as ethylene glycol as well as those more complex compounds comprising two hydroxy groups attached to a chain containing both carbon and oxygen atoms, such as triethylene glycol, tetraethylene glycol and polyethylene glycol, for example, of 4,000 daltons molecular weight. Triethylene glycol and especially tetraethylene glycol are of particular interest in view of their very low toxicity. By using such glycols and glycol ethers it is possible to increase solubility for many complexes to 10 to 20 mg/ml.

In the treatment of loss of calcium from bone due to periodontal disease the gallium compound may administered topically in an intra-oral formulation comprising, for example, a highly concentrated rinse, gel, or other pharmaceutically acceptable carrier for the local treatment of periodontal disease.

DOSAGES AND DOSAGE FORMS

Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions containing a unit dose, or a multiple or sub-unit dose. While the dosage of hydroxypyrrone gallium complex given will depend on various factors, including the particular compound which is employed in the composition, it may be stated by way of guidance that maintenance at a satisfactory level of the amount of gallium present in the human body for the treatment purposes

described previously, will often be achieved using a daily dosage, in terms of the gallium content of the compound, which lies in a range from about 0.1 to 100 mg and often in a range from 0.5 to 10 mg, for example 1 or 2 mg. However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels.

In general, the aim should be to provide the amount of gallium required by the patient without administering any undue excess and the properties of the pharmaceutical compositions according to the present invention are particularly suited to the achievement of this aim. Similarly, the concentration of gallium in the pharmaceutical composition in the form of the hydroxypyrrone complex may vary quite widely, for example over a range from about 0.001 to about 20% w/w. However, it is more usual for the concentration to exceed 0.01% w/w and it may often exceed 0.05 or 0.1% w/w, while a more usual limit for the upper end of the range is about 13% w/w. A common range of concentration is 0.05 to 5% w/w, for example 0.2 to 0.5, 1 or 2% w/w.

This invention is illustrated by the following examples:

EXAMPLE 1 - Preparation of Gallium Maltol Enteric Coated Capsule

A preparation of gallium maltol in admixture with maltol (containing 1 part by weight of gallium to 10 parts by weight of maltol) is obtained by the addition of a 1M ethanolic solution of gallium chloride to a methylene chloride solution of the appropriate amount of maltol, followed after 5 minutes at 20° C. by treatment with a 10 molar excess of solid solution carbonate, stirring for 10 minutes, filtration and evaporation of the solvents.

The resulting solid gallium maltol preparation is divided into 50 mg quantities and added to standard gelatine capsules (16 x 5 mm), each capsule containing 5 mg of

gallium. The capsules are then coated with a cellulose acetate phthalate/diethylphthalate layer (6 mg coat per cm² of capsule surface) in a small scale procedure analogous to the procedure described by Jones, *ibid*. A proportion of the capsules are treated to add a second similar coating. Such capsules are resistant to dissociation in the stomach but will undergo dissociation in the intestine. Thus, when treated at 37° C. with dilute aqueous hydrochloric acid (pH 2.0) the singly coated capsules are typically stable for 30 minutes but in Krebs Ringer bicarbonate solution (pH 7.4) at 37° C. they dissociate to release the gallium complex within 1 minute. The doubly coated capsules are typically stable at pH 2.0 for 20 hours, again dissociating within 1 minute at pH 7.4.

EXAMPLE 2 Liposome Formulation of Gallium Maltol

(A) a solution of egg yolk phosphatidyl chlorine (40 mg) and cholesterol (40 mg) in chloroform (1 ml) is rotary evaporated in a 50 ml round bottomed flask to form a thin lipid film. An aqueous solution of the 3:1 neutral gallium maltol complex (6 ml, 1 mg/ml) is added to the flask and the mixture is vibrated for 15 minutes. Centrifugation (3,000 rev/minute for 10 minutes) yields multilammellar liposomes containing gallium maltol.

(1) In a modification of this procedure the phospholipid may be varied among egg yolk phosphatidyl chlorine, dimyristoyl phosphatidylcholine and dipalmitoyl phosphatidylcholine together with a preparation of cholesterol varying from 0 to 1 moles of cholesterol per mole of phospholipid.

(B) A chloroform solution (2 ml) of the 3:1 neutral gallium maltol complex (5 mg/ml) is added to egg yolk phosphatidylcholine (100 mg) and a cholesterol (50 mg). The solution is rotary evaporated to yield a deep red skin on the surface of a round bottomed flask. Addition of 6 ml of a buffered solution of sodium chloride (100 mM, Tris.HCl:

20 mM, pH 7.4) followed by shaking for 15 minutes leads to a finely dispersed lipid-gallium maltol preparation. Centrifugation at 3000 revs/minute for 100 minutes yields a liposome preparation which can be readily freeze dried. The entrapment of gallium maltol using this method is particularly efficient.

Liposomes produced by either method are resistant to dissociation in the stomach but will undergo dissociation in the intestine.

EXAMPLE III - Rat Model Bioavailability Study

Gallium maltol complex was administered to laboratory rats, (1) intravenously, (2) directly to the intestine, or (3) into the stomach. In some rats the proximal region of the duodenum was ligated (double ligation, 1 cm apart at the pylorics) under anesthesia. About 20 minutes after recovery from the anesthesia, an aqueous solution of gallium maltol complex was injected, intravenously, into the duodenum (below the ligation), or into the stomach (above the ligation). To assess drug absorption, serial blood samples for serum preparation were collected primarily from the tail vein. The samples were taken 0.5, 0.75, 1.0, 2.0, 3.0, and 4.0 hours after administration of the dose. The apparent oral bioavailability was calculated based upon the following formula wherein AUC means "area under the plasma concentration v. time curve from zero time to 4 hours post-dose."

$$F = \frac{\text{AUC intestinal or stomach,}}{\text{AUC iv}}$$

after correction for equivalent doses.

Figure 1 shows the results of the serum sampling, in terms of the concentration of the gallium in the blood. As can be seen from that Figure, introduction directly into the intestine achieved a blood serum level essentially identical

to that achieved through intravenous injection. The introduction directly into the stomach, without ligation, provided the next highest level of serum availability, as the gallium complex under such conditions could pass, in part, into the intestine. This comparative performance is shown graphically in Figure 2. Table I contains the numerical data calculated for the foregoing experiment for each laboratory rat studied and Table II contains the summary data for each rat grouping, based upon the route of administration

The fact that the administration of the gallium complexes directly into the intestine could achieve a blood level approximately equal to 80 percent of that achieved through intravenous injection is truly unexpected and surprising.

TABLE I

Rat #	Route of Administration	AUC 0-4 hr (ng/ml)hr	Bioavailability %
12	IV	10,707	100
13	IV	6,369	100
14	IV	9,678	100
3	Intestine (1 ligation) ^a	4,916	55
7	Intestine (1 ligation) ^a	3,479	39
8	Intestine (1 ligation) ^a	17,022	129
9	Intestine (1 ligation) ^a	10,666	96
5	Intestine (1 ligation) ^a	6,980 (6,941, 7,019)	78 (78, 79)
1	Stomach (no ligations)	813	9
2	Stomach (no ligations)	4,008	45
4	Stomach (no ligations)	5,535 (5,226, 5,843)	63 (59, 66)
6	Stomach (1 ligation) ^a	114	1
10	Stomach (1 ligation) ^a	173 (166, 179)	2 (2, 2)
11	Stomach (1 ligation) ^a	213 (154, 272)	2 (2, 3)

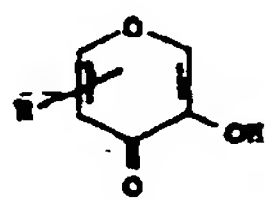
^aAll ligation(s) made at the pylorus.

TABLE II

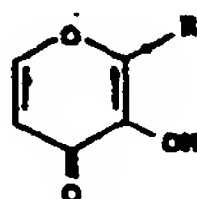
Drug (mmol/kg)	Route of Administration	Ligation	No. of Rats	%Bioavailability
JM 2118 (0.067)	IV		3	100
	Intestine	1	4	39, 55, 96, 129
		2	1	78
	Stomach	0	3	9, 45, 63 1, 2, 2

What is claimed is:

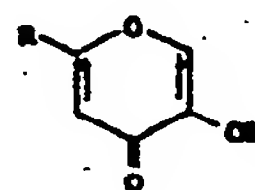
1. A method effective against excessive loss of calcium from bone in a human individual requiring such treatment comprising orally administering to the individual an effective amount of composition comprising a pharmaceutically acceptable gallium compound complexed with a ligand of the formula



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II



III

in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition.

2. The method of claim 1 wherein said excess loss is due to hypercalcemia.

3. The method of claim 1 wherein said excess loss is due to osteopenia or osteoporosis.

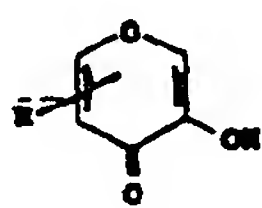
4. The method of claim 1 wherein said excess loss is due to bone metastasis from malignant tumors.

5. The method of claim 1 wherein said excess loss is due to hyperparathyroidism.

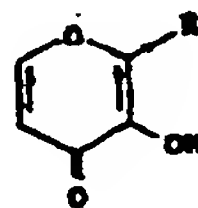
6. The method of claim 1 wherein said excess loss is due to periodontal disease and said gallium compound is administered intra-orally in a topical formulation comprising a concentrated rinse, gel or other pharmaceutically acceptable carrier.

7. A method effective against excessive loss of calcium from bone in a patient requiring such treatment comprising orally

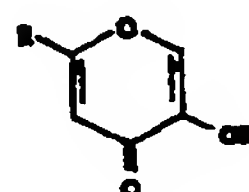
administering to said patient an effective amount of a pharmaceutically acceptable composition comprising a gallium compound complexed with ligands of the formula



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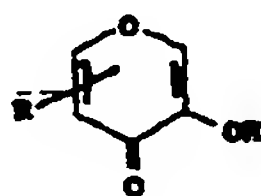
II



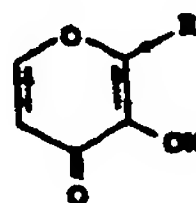
III

in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition.

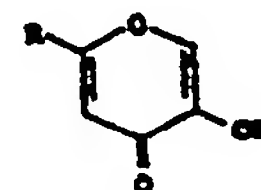
8. A method effective against bone pain due to excessive loss of calcium from bone in a human individual requiring such treatment comprising administering to the individual an effective amount of composition comprising gallium complexed with ligands of the formula



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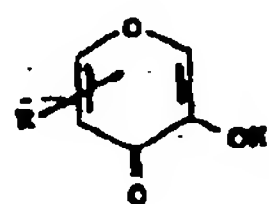


III

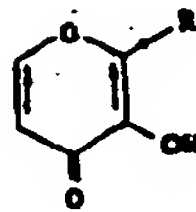
in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition.

9. A method effective against bone fractures due to excessive loss of calcium from bone in human a individual requiring such treatment comprising administering to the individual an effective amount of a composition comprising

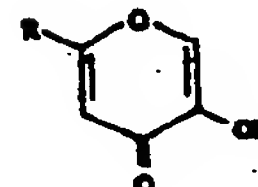
individual an effective amount of a composition comprising gallium complexed with a ligand of the formula



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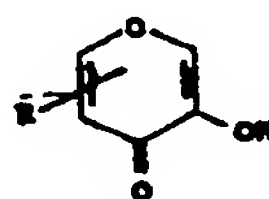
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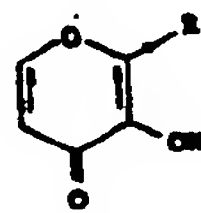
III

in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition.

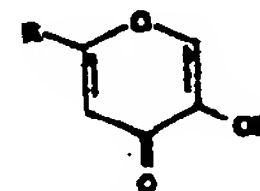
10. A method for the treatment of malignant tumors in a mammal comprising administering to said mammal by the oral route a pharmaceutically effective amount of a composition comprising gallium complexed with a ligand of the formula



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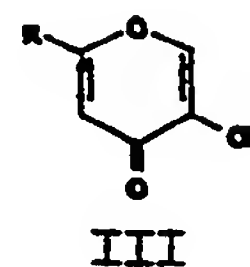
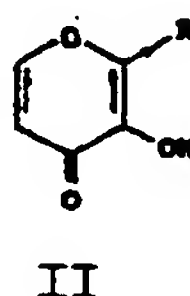
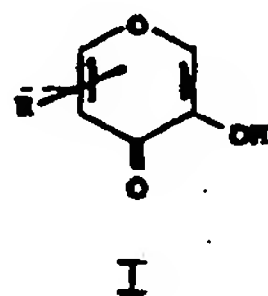
II



III

in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition.

11. A composition comprising gallium and non-radioactive indium wherein the gallium is in the form of a complex with a ligand of the formula

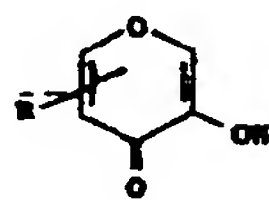


in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition.

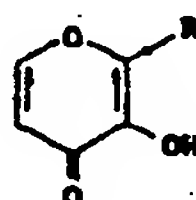
12. A composition according to claim 11, wherein said gallium is gallium-67 or gallium-68.

13. A pharmaceutical composition comprising a gallium complex in which each ligand is provided by the same or a different compound selected from the group consisting of 3-hydroxy-4-pyrones in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by a hydrocarbon group of 1 to 6 carbon atoms, excluding complexes in which each ligand is provided by 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone or 3-hydroxy-6-methyl-4-pyrone, and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine.

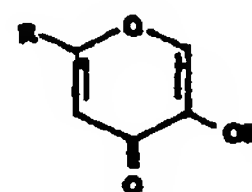
14. Use of a composition comprising a pharmaceutically acceptable gallium compound complexed with a ligand of the formula



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in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition, in the manufacture of a medicine for the treatment against excessive loss of calcium from bone in a human individual requiring such treatment.

15. The use of the composition of claim 14 wherein said excess loss is due to hypercalcemia.

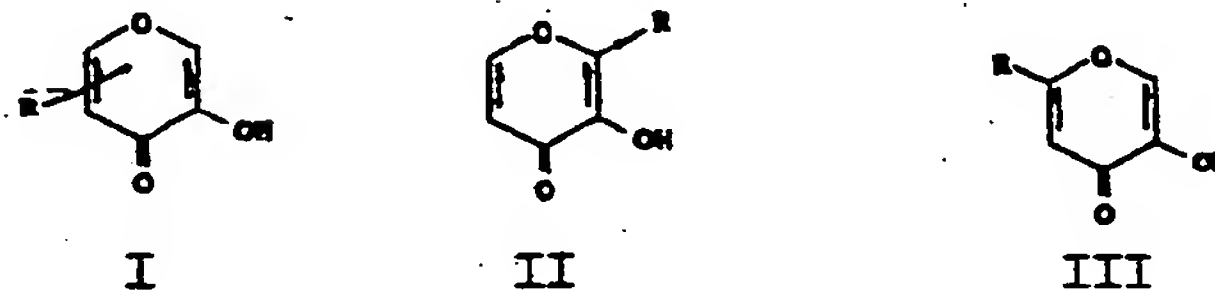
16. The use of the composition of claim 14 wherein said excess loss is due to osteopenia or osteoporosis.

17. The use of the composition of claim 14 wherein said excess loss is due to bone metastasis from malignant tumors.

18. The use of the composition of claim 14 wherein said excess loss is due to hyperparathyroidism.

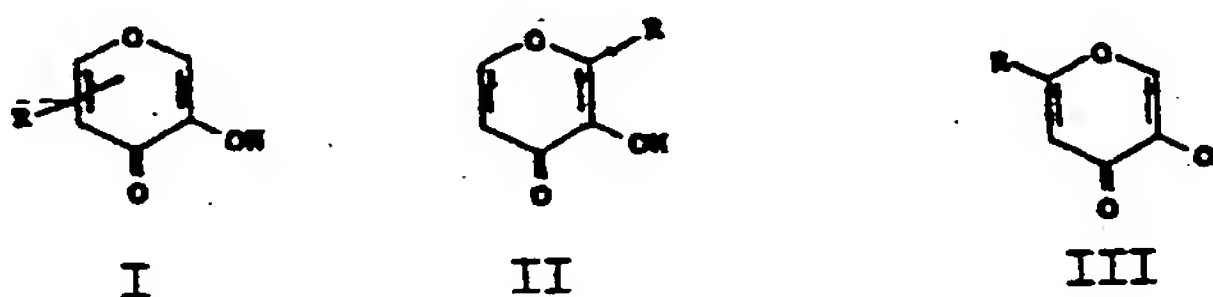
19. The use of the composition of claim 14 wherein said excess loss is due to periodontal disease and said gallium compound is administered intra-orally in a topical formulation comprising a concentrated rinse, gel or other pharmaceutically acceptable carrier.

20. Use of a composition comprising a pharmaceutically acceptable gallium compound complexed with a ligand of the formula



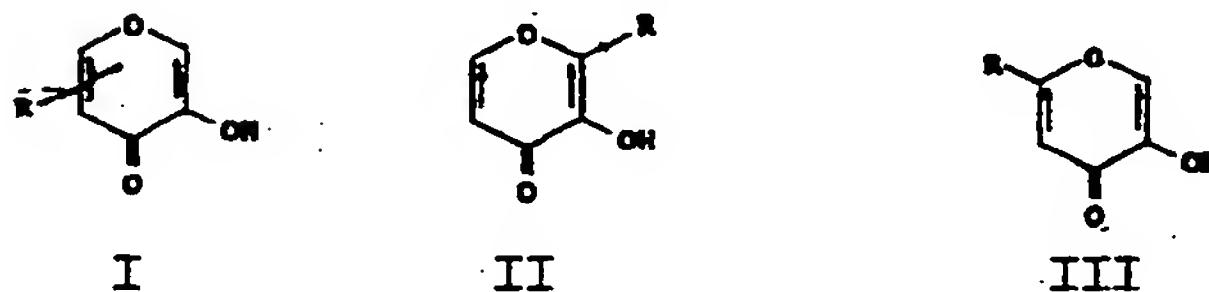
in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition, in the manufacture of a medicine for the treatment against bone pain due to excessive loss of calcium in a human individual requiring such treatment.

21. Use of a composition comprising a pharmaceutically acceptable gallium compound complexed with a ligand of the formula



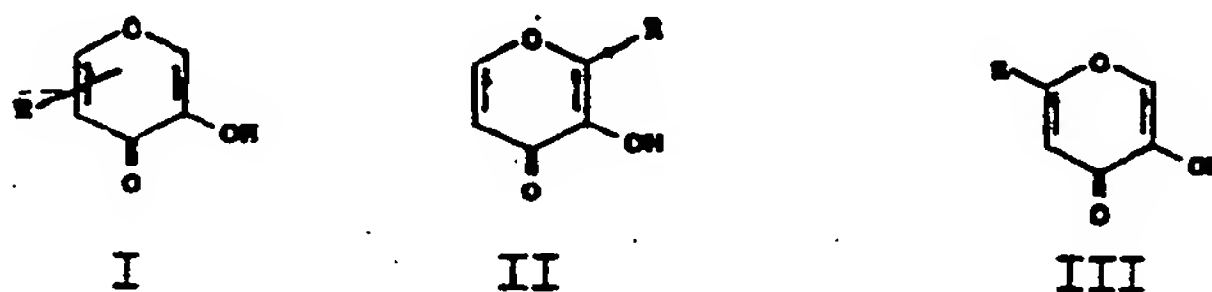
in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition, in the manufacture of a medicine for the treatment against bone fractures due to excessive loss of calcium from bone in a human individual requiring such treatment.

22. Use of a composition comprising a pharmaceutically acceptable gallium compound complexed with a ligand of the formula



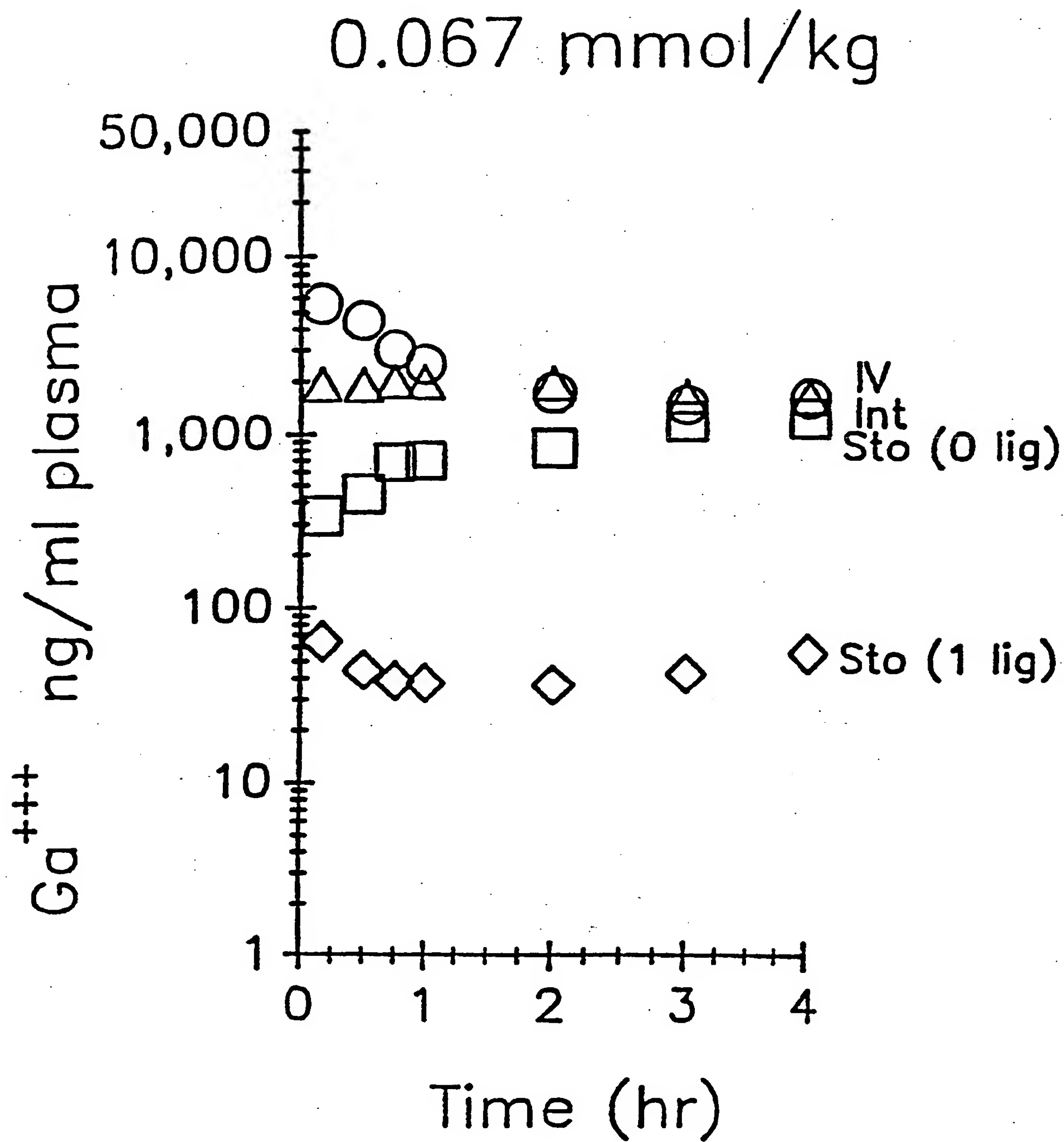
in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition, in the manufacture of a medicine for the treatment against malignant tumors in a mammal requiring such treatment.

23. Use of a composition comprising a pharmaceutically acceptable gallium compound complexed with a ligand of the formula



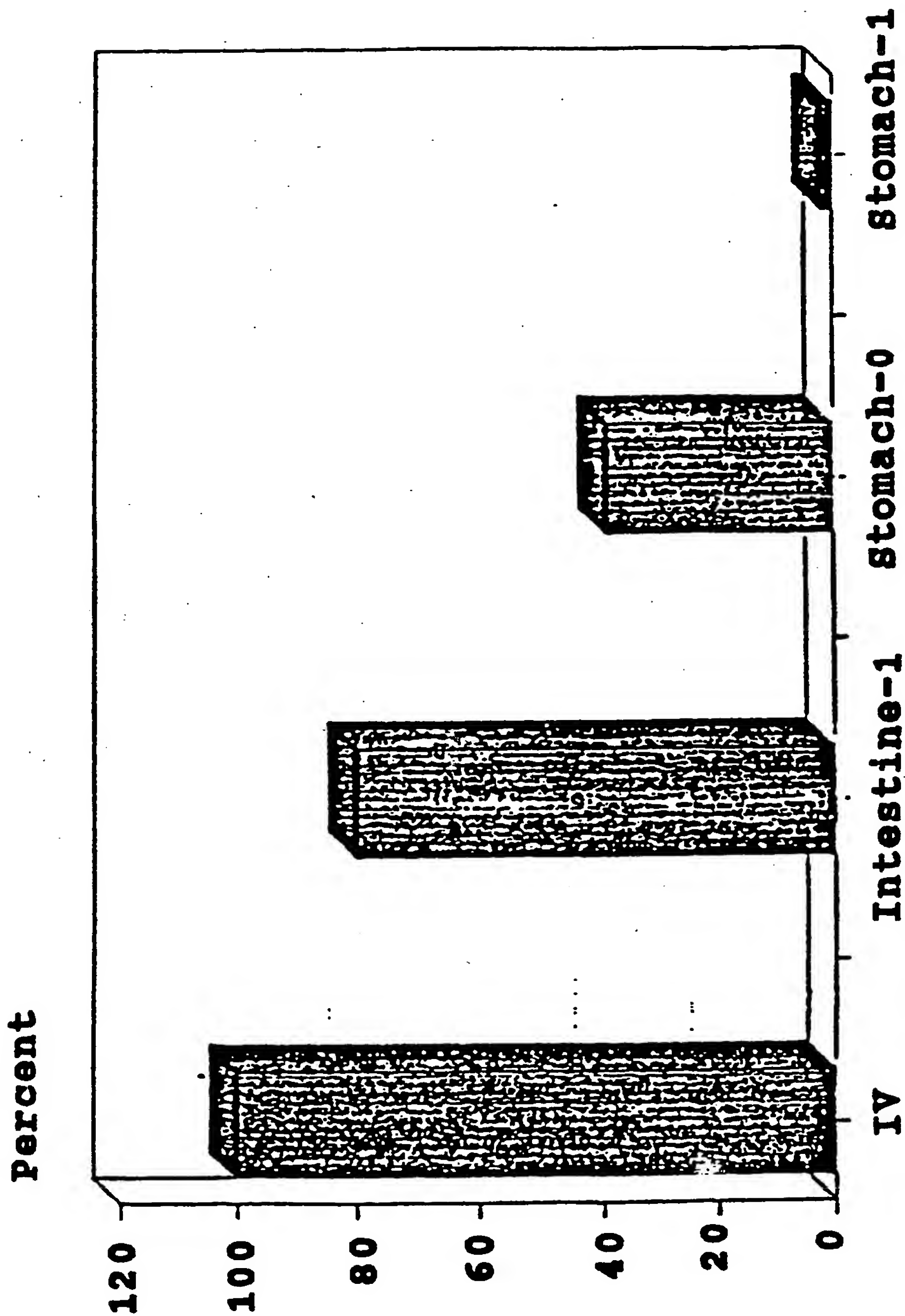
in which R is a hydrocarbon group containing from about 1 to about 6 carbon atoms and non-radioactive indium wherein said composition inhibits dissociation of the gallium complex in the stomach while allowing release of the gallium complex in the intestine, after oral administration of said composition, in the manufacture of a medicine for radiographic imaging in a mammal requiring such treatment.

FIG. 1



SUBSTITUTE SHEET

FIG. 2
Effect of Injection Route & Ligation No.



0 and 1 designate # of ligations

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/03599

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): A61K 31/555, 33/24, 43/00, 49/02		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
US	424/650,1.1; 514/184	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
STN Messenger, Text Search, Files BIOSIS and CA APS Messenger, Text Search, File USPAT		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 4,448,763 (TRIPLETT) 15 May 1984 See column 2, line 50 bridging column 3, line 37.	11,12
Y	US, A, 4,529,593 (WARRELL, JR et al.) 16 July 1985 See col. 1, lines 61-65; and col. 2, lines 10-39.	1-23
A	US, A, 4,575,502 (HIDER et al.) 11 March 1986	
A	US, A, 4,591,506 (BONADIO) 27 May 1986 See col. 2, lines 25-68.	
Y	US, A, 4,596,710 (COLLERY) 24 June 1986 See col. 1, lines 3-28.	11,12
Y	US, A, 4,704,277 (BOCKMAN et al.) 03 November 1987 See claims 1 and 9.	1-23
Y	Farrar et al., "Tissue Distribution of Gallium Following Administration of the Gallium-Maltol Complex in the Rat: A Model for an Aluminum-Maltol Complex of Neurotoxicological Interest", J. Food	1-23
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
31 JULY 1991		19 AUG 1991
International Searching Authority		Signature of Authorized Officer
ISA/US		 JOHN M. COVERT

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	<u>Chemistry Toxicology</u> , vol. 26(6), 1988, 523-525 (Eng).	
A	Finnegan et al., "Neutral Water-Soluble Post-Transition-Metal Chelate Complexes of Medical Interest: Aluminum and Gallium Tris (3-Hydroxy-4-Pyronates", <u>J. Inorg Chem.</u> , vol. 26(13), 1987, 2171-2176 (Eng).	
E	J.W. Babich et al., "3-Hydroxy-4-Pyrones: Evaluation of a New Class of Bidentate Ligands for the Membrane Transport of Gallium and Indium", <u>J. Labelled Compounds and Radiopharmaceuticals</u> , 1991, 30(0), 63-65 (Eng).	1-23
A	Farrar et al., "The Intestinal Adsorption and Tissue Distribution of Aluminum, Gallium and Scandium: A Comparative Study", <u>Biochem. Soc. Trans.</u> , 1967, 1164-1165 (Eng).	